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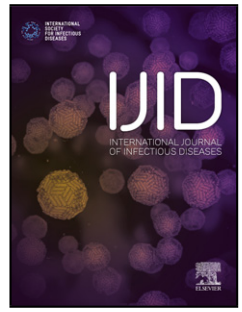

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Highlights

- Correlation between hypothermia and death in review of SARS-CoV-2 cases
- Probability of death was 2.06 times higher for those with hypothermia
- Hypothermia useful as predictor of mortality in SARS-CoV-2
- Information can assist in resource allocation management

Abstract

Objective:

We observed patients to have variable temperatures. The objective of the study was to identify if hypothermia in a patient infected with SARS-CoV-2 is associated with a higher than expected mortality.

Methods:

We reviewed 331 charts from patients hospitalized with SARS-CoV-2 between March 9 to April 20, 2020.

Results:

The probability of death was 2.06 times higher for those with hypothermia than those without [95% C.I. (1.25, 3.38)]. In ventilated patients, there were 32 deaths. Of those, 75% had been hypothermic. In a prior review of 10,000 non-SARS-CoV-2 patients with sepsis, the mortality rate in patients with hypothermia was 47%. Reviewed studies demonstrated a range of expected mortality rates in patients with ventilator dependent respiratory failure and sepsis. In comparison, our study shows that within a group of critically ill patients with SARS-CoV-2 and hypothermia, the mortality rate exceeded those rates.

Conclusion:

Our review showed a significant association between hypothermia and death ($p=0.0033$). Predictors of mortality in SARS-CoV-2 disease can expedite earlier aggressive care. Additionally, in areas with limited resources or overburdened healthcare systems, there may be a need for resource allocation management and information about mortality risk may be helpful.

Keywords: Hypothermia; SARS-CoV-2; outcome

Introduction

In the current SARS-CoV-2 pandemic, it has been important to identify features in the clinical presentation that would serve as indicators of disease progression. There were 21,813,451 diagnosed cases of SARS-CoV-2 throughout the world as of August, 16, 2020 with 5,564,376 of those cases in the United States. As of April 26, 2021, there are 148,442,514 million cases with the numbers continuing to rise (COVID-19 Coronavirus Pandemic 2020). There have been times throughout the pandemic where we have been faced with limited resources specific to Remdisivir and Convalescent plasma, treatment options which have shown potential to be beneficial (Grein et. al, 2020, Joyner et.al, 2020). Studies are ongoing to verify the efficacy of these interventions. As providers we worried about the possibility of having to scale patients in order to determine who could receive those treatments. This concern did not manifest as a reality in our center, but it came close. However, we surmise that in resource poor areas, or in the event of a large surge of patients, this could become a necessity. Fever has been identified as one of the hallmark presenting symptoms used as a marker for whom to screen for this infection. However in patients with this infection, temperature readings vary. During the course of our clinical care of patients with SARS-CoV-2 we identified patients with hypothermia, normothermia and hyperthermia. The number of patients with hypothermia seemed to exceed the number typically seen during the course of our clinical care of patients with infection and sepsis. Our study sought to further investigate this observation.

Hypothermia is sometimes utilized as a therapeutic effort in sustaining the life of a person who presents with cardiac arrest. Likewise, hypothermia can be induced in trauma patients in an effort to spare tissue damage (Hildebrand 2004). The decline in temperature is associated with a decrease in metabolic rate which can be protective against ischemia (Sailhamer 2007). Accidental hypothermia is an unintentional decrease in temperature in a person who does not have obvious intrinsic thermoregulatory dysfunction. This form of hypothermia may be as a result of excessive cold exposure (Hildebrand 2014). Hypothermia as it relates to our review is that which can be seen in sepsis and is felt to a consequence of impaired thermoregulation. The etiology of this is described as a "failure of the hypothalamus to regulate the core body temperature" (Faulds 2013). There may be an alteration in the baseline temperature setpoint by the hypothalamus as a result of sepsis or severe infection. Alternatively it may be a nonspecific response due to widespread systemic inflammation (Leon 2004).

Sepsis is the body's harmful systemic reaction to microbial infection. Hypothermia has been clearly associated with sepsis. ICU and hospital mortality have been identified as being higher in septic patients with hypothermia (Wiewal 2016). Fever or hypothermia can be symptoms identified in any degree of sepsis. In 2017 a meta-analysis of studies was performed looking at temperature and mortality rates in patients with sepsis. Approximately 10,000 cases of sepsis were reviewed. The reviewers found that septic patients with fever had an estimated mortality rate of approximately 22%. The estimated mortality rate in patients with normal temperature was 31% and the highest estimated mortality rate of 47% was found in hypothermic patients (Rumbus, 2017).

Admission to the ICU for SARS-CoV-2 patients is associated with a high mortality rate, ranging from 16 to 78%, with an Italian review of 3,988 patients showing a mortality rate of close to 50% (Grasselli 2020). Understanding that ICU patients at a baseline have a high mortality, we are looking to discover what impact hypothermia has on the SARS-CoV-2 patients.

We expect to see a higher mortality rate in SARS-CoV-2 patients with hypothermia. We are interested in how significant this association is and if there are any significant correlations with age, weight, oxygen requirement or inflammatory markers.

Review of literature

In 1868, Carl Reinhold Wunderlich measured body temperature in about 25,000 people and established a normal temperature as 98.6 °F and an elevated body temperature as 100.4 °F (Mackowiak 1998).

Hypothermia is defined as a core temperature <35 °C (95 °F) and is further classified as follows: mild 35 °C to 32 °C, moderate 32 °C to 28 °C, severe 28 °C to 20 °C, and profound <20 °C (Fagenholz 2013). Body temperature is closely regulated through a balance between heat production and heat dissipation. The pre-optic nucleus of the anterior hypothalamus is the thermal control center. In response to a decrease in core body temperature, the hypothalamus initiates mechanisms to conserve heat including shivering, and non shivering thermogenesis (increased activity of thyroxine and catecholamines). However, as the core temperature decreases below 35°C (95°F), the coordinated systems responsible for thermoregulation begin to fail (Kobeissi 2014). Proinflammatory cytokines including interleukin-6, interleukin-1 and TNF-alpha play a crucial role in the genesis of a fever. However, there appears to be no correlation between decreased circulation of these cytokines and hypothermia (Marik 2000, Wiewel 2016). The mechanism of hypothermia in sepsis is unclear, however, many studies agree that hypothermic patients with septic shock have a significantly higher mortality rate and higher incidence of organ dysfunction compared to patients who mount a febrile response (Kushimoto 2013).

Early case reports pointed out fever as a common presenting symptom for SARS-CoV-2 infection, as commonly seen with other viral infections. In a meta-analysis of 3,062 patients with SARS-CoV-2, fever was noted in 80.4% of the patients (Zhu et al.,2000). Acute hypothermia has been described in a SARS-CoV-2 as a case report (Allard 2020).

Methods

We retrospectively reviewed the medical records of 331 patients who had been hospitalized at Broward Health Medical System hospitals. We looked at the clinical outcomes of these adult patients with laboratory confirmed SARS-CoV-2 infection. The patients were hospitalized and treated for SARS-CoV-2 infection between March 31, 2020 to April 20, 2020. Our Institutional Review Board granted full waiver for this retrospective chart review research project. Data points we reviewed were temperature, age, oxygen requirements, inflammatory markers, weight, underlying medical conditions and outcomes. Five physicians reviewed the medical records. We documented the age, body mass index (BMI), oxygen requirement, measures of C reactive protein, D dimer, Ferritin and their outcome (discharge, discharge with oxygen, death). Statistical analysis was utilized to assess for any significant associations.

Statistical Analysis and Results

Analysis 1: Hypothermic Status: Outcomes

These data contained only hypothermia patients, and so a regression to determine the effect of hypothermia on the odds of death, relative to other patient-specific variables, could not be performed. However, a frequency analysis was performed using the categories of Hypothermia (versus not) and Death (versus not) as outlined in the Summary tab of the file. In all cases, a significance level of 0.05 was used.

A Fisher's Exact Test was performed on the above frequency table, indicating that there is a significant association between Hypothermia and Death (p=0.0033). In particular, the probability of death was 2.06 times higher for those with Hypothermia than those without [95% C.I. (1.25, 3.38)].

Analysis 2: Hypothermic Status of Deceased Patients: Steroid Administration

Although Regression is preferable when dealing with multiple possibly-related independent variables, the count statistics associated with individual categorical variables can be useful. In all cases, p-values represent the outcome of either a Chi-squared or Fisher's Exact test, as appropriate.

The following analysis was performed checking for variable interactions within the regression and contingency tables, analyzing differences between deceased patients who were hypothermic versus not, and relationship between deceased patients having hypothermia and use of steroids.

There was also no statistically significant association between hypothermia status and steroid administration (Table 3):

Analysis 3: Hypothermic Status of Deceased Patients: Multinomial Logistic Regression

An exhaustive search of all linear and interactive models yielded no statistically significant predictors of hypothermia in deceased patients, among all variables considered above.

There were no statistically significant relationships found between elevated c-reactive protein (CRP) at a level of greater than 1.0 ug.dl, elevated ferritin at a level of >275 ng/ml, elevated body mass index (BMI) greater than or equal to 30 with respect to category and discharge status for the hypothermic patients in this study.

Discussions/Conclusions

The proposed pathophysiological mechanism of sepsis in SARS-CoV-2 associated infections is complex and typically involves patients with severe disease. A cytokine response syndrome has been identified as the precursor to shock in cases of severe disease, however, the virological mechanism remains unidentified for the time being. Inference of the exact process has been drawn from similarities in severe disease seen with influenza which involves the release of cytokines in lung epithelial cells. Elevated temperatures can augment aspects of humoral and cellular immunity (Launey et al., 2011). However, a percentage of septic patients present with hypothermia rather than hyperthermia. Similar to hyperthermia, studies have shown that hypothermia is associated with an increased risk of mortality in sepsis (Young et al., 2012). In our review we used a cutoff of 35.8°C (96.5°F) to define hypothermia. Allard, et al. (2020)

describe acute hypothermia in a patient with SARS-Cov2 infection and this is something we saw in 34% of the cases we reviewed.

The Recovery Trial (2020) showed a reduction in 28 day mortality among those who received glucocorticoid class drug, dexamethasone. This study was published after the date of most patients whose charts we reviewed. However, we still found that patients had received hydrocortisone or solumedrol, more often later in the course of their hospitalization. It is known that the use of glucocorticoids affects body temperature and can result in hypothermia (Kaimuma 2009). We therefore took into consideration the effect of steroid use in patients in our review who had expired. Of the 39 Hypothermic patients who died, 21 (53.8%) received steroids and 18 (46.1%) did not. Of the 24 Non-Hypothermic patients who died, 9 (37.5%) received steroids and 15 (62.5%) did not. Statistical analysis did not reveal any statistically significant association between hypothermia and steroid administration.

A review of 624 patients diagnosed with severe sepsis showed that patients with hypothermia as defined by a temperature of less than 36.5°C on presentation had worse sequential organ failure assessment scores compared to those with a temperature above 36.5°C. The 28 day and in hospital mortality was found to be higher in the group with hypothermia (Kushimoto et al., 2013). In reviewing our results, looking at the category of ventilated patients, there were 32 deaths (Table 1). Of those deaths, 75% of the patients had been hypothermic. In a prior review of 10,000 non-SARS-CoV-2 patients with sepsis, the mortality rate in patients with hypothermia was 47%. Reviewed studies demonstrated a range of expected mortality rates in patients with ventilator dependent respiratory failure and sepsis (Rumbus 2017). In comparison, our study shows that within a group of critically ill patients with SARS-CoV-2 and hypothermia, the mortality rate exceeded those rates. A comparison of critically ill patients with SARS-CoV-2 and sepsis patients from historical data can be made as the SARS-CoV-2 patients met some or all criteria for the diagnosis of sepsis, particularly when in the intensive care unit. While we understand that the mere presence of hypothermia indicates that a patient is severely ill, the findings that there is a statistically significant association between hypothermia and death in the SARS-CoV-2 population can be used as an indicator of poor outcome. Throughout the pandemic, we have been faced with limited resources such as the antiviral Remdisivir, or convalescent plasma. Having a better understanding of potential patient outcomes, this information can be utilized to assist in resource management.

Our review identified a significant association between hypothermia and death ($p=0.0033$). In particular, the probability of death was 2.06 times higher for those with hypothermia than those without [95% C.I. (1.25, 3.38)]. Older, heavier patients or with one or more underlying medical conditions (data not shown) were no more prevalent among hypothermic patients who died. In our review we identified that among the hypothermic patients, the percentage of patient death increased as the D-dimer category level increased. Although these associations were statistically significant, causality cannot be inferred. Previous reports have noted this, and autopsy correlation has been documented. A comprehensive literature review performed by Sakka, et al. (2020) identified elevated D-dimer levels significantly associated with the risk of mortality. Thrombosis of small and mid sized arteries were seen in a pathology case series from autopsies on 11 patients who had died from SARS-CoV-2 infection (Lax, et al. 2020). Our study demonstrates what has been detailed by Yao, et al., that D-Dimer does serve as a biomarker for disease severity.

The National Institute of Health treatment guidelines include a report indicating possible side effects of hypothermia in association with convalescent plasma transfusion (NIH 2021). We therefore reviewed our data looking to see if there was any correlation in the patients between receipt of convalescent plasma and hypothermia. We did not find any causal relationship.

We would recommend that patients with hypothermia be recognized as being at higher risk for poor outcome, particularly if intubated. Our report describes our single institutions experience and might not be generalized to other institutions or locations. Additional study is warranted to verify these results and identify a larger comparator group.

Funding:

No funding was obtained for this study.

Ethical Approval:

The Institutional Review Board of Broward Health Medical Center reviewed and approved this study.

Conflict of Interest Statement:

The authors whose names are listed immediately below certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript. The authors whose names are listed immediately below report the following details of affiliation or involvement in an organization or entity with a financial or nonfinancial interest in the subject matter or materials discussed in this manuscript.

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Table 1: Parameters Reviewed from Charts of SARS-CoV-2 Patients

Temperature	Hypothermia < or = 96.5°F	Hyperthermia > or = 100.4 °F	
Oxygen requirements	Room Air	Oxygen Supplementation	Ventilator
D Dimer	<0.5 ug/ml	0.5-3.0	>3.0
Ferritin	<275 ng/ml	> or = 275	
C Reactive Protein	>1.0 mg/dl		
Weight	BMI 18-29	BMI > or = 30	
Outcomes	Discharge	Discharge with O2	Death

Table 2: Hypothermic Status and Outcomes

	Dead	Alive	*% Dead*
Hypothermic patients	39	96	*28.9%*
Not hypothermic patients	43	218	*16.5%*
% Hypothermia	*47.6%*	*30.6%*	

Table 3. Steroid Administration

	Yes	No
Hypothermic patient	21 (70.0%)	18 (54.5%
Non-Hypothermic patient	9	15